The new therapeutic age: Biotherapeutics

Biotherapeutics: characteristics and impact.
Biotherapeutics: manufacturing processes.
Biosimilar: similar is not the same as equal.

Differences you must know between Chemically-synthesized and Biotherapeutics
Biosimilars: the key to be similar is comparability.
Biotherapeutics and Biosimilars: safety as a challenge.
Biotherapeutics: a new challenge for Pharmacovigilance
Risk in the use of Biosimilars: how to manage it

AGENDA

Active ingredient of a drug: the name identifying it
International Nonproprietary Name according to WHO
International Nonproprietary Name (INN) for biosimilars

Interchange a Innovative Biotherapeutic with a Biosimilar drug
Pharmacovigilance: an essential support for interchangeability
Bases for safe interchangeability in Biosimilars
New therapeutics: Biotherapeutics or Biodrugs

- They are drugs obtained from tissues, cells or fluids of animal or vegetable source through genetic manipulation.
- They are produced through complex biotechnological processes in special plants where other drugs are not produced.
- They are administered only by injection, infusion or recently oral use.

Biotherapeutics: it is based on drugs of a biological origin.

It is used in chronic and serious diseases such as Diabetes, Cancer, Rheumatoid Arthritis and other.

For these patients, it brings therapeutical hope.

Drugs commonly used by us are of chemical origin, produced through chemical synthesis in large plants and manufactured in all pharmaceutical forms (tablets, creams, syrups, liquids.)

Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology.
Biotherapeutics: characteristics and impact.

What are proteins of Biotherapeutics like

- They are macromolecules (large molecules)
- They have a very unstable chemical structure (they may change during the production process)
- They are almost identical to body molecules
- Their 3D structure is very complex

Slight changes in these molecules may cause:

- Changes in efficacy
- Safety alterations

EMA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Dec 2014
Good Pharmacovigilance Principles and Considerations for Biotherapeutic Medicines. IFPMA 2015
Biotherapeutics: manufacturing processes as a variable with an impact on patient safety

- Production of these drugs implies biological processes and materials, like cell culture.

- Raw material contamination is possible and therefore purification processes are a must.

- Manufacturing processes are very complex and any change, no matter how small, has an impact on the final result.

- They involve numberless production steps. They require many complex control analyses for each step, by specialized staff.

- Given the complexity and number of production steps, the likelihood of finding small differences between lots rises. This is why a lot could be different from another and therefore every lot administered to patients has to be monitored.
Differences you must know between Biotherapeutic antibody from design to production

**Chemically-Synthesized molecule**
- Produced by chemical synthesis
- Analyzed by standardized chemical methods
- Bioequivalence

**Biotherapeutic antibody**
- Produced by complex biotechnological processes
- Subject to complex analytical methods
- Clinical trials
- Patient follow-up plan obligatory throughout the marketing process.

EMA: Questions and answers on generic medicines, Nov 2012
Biosimilar: it is a new term about which there is much debate around the world.

There is not only one definition; it is defined by the characteristics that Health Agencies require to approve it as a biosimilar.

A biosimilar is a drug that is similar to a biological drug already being marketed (reference drug).

Warning:
A biosimilar is not the “generic” of a biological drug. The term generic only applies to chemically derived medicinal products.

Biosimilar

The active ingredient is almost the same biological substance as the reference drug, except for minimum differences in origin and production methods.

It comes from a cell line (strain) that is different from the reference drug (original biodrug).

It has the same indications as the reference drug.

Compared with the reference product, it is similar in quality, efficacy and safety.

Because it is a biological product, it has some natural variability, just like the reference product.

EMA, Guideline on similar biological medicinal products. Oct 2014
How to differentiate them?

Biotherapeutic Medicine
A medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

Biosimilar
- Product highly similar to a biotherapeutic medicine that has already been authorized with full dossier.
- Subject to a tailored regulatory data package with full side-by-side analytical and clinical testing.
- Minor variations compared to the original biotherapeutic reference product with no clinically meaningful differences identified.

Non-comparable Biotherapeutic
- Product claiming to be copy of another biotherapeutic medicine yet not approved in alignment with WHO standards.
- A non-comparable biotherapeutic is:
  - Developed with limited side-by-side comparison proving biosimilarity to reference product.
  - Product with unclear approval standards, thereby posing potential risk to patients and public health.
Biosimilars: the key to be similar is comparability

Comparability that determines similarity with the reference product must be shown in all the biosimilar development stages. When comparability is not convincing, a special clinical trial called “equivalence design controlled” must be conducted.

Efficacy and safety
Confirm Biocomparability

Clinical Phases

Pre-clinical

Establishing comparability

First objective:

Comparability of the biological activity
Physical-chemical comparability

Define reference product
Characterization
It is the process to know the reference drug components in detail

CHMP/437/04 Rev 1 Committee for Medicinal Products for Human Use (CHMP)
Guideline on similar biological medicinal products, 23 October 2014
Biotherapeutics and Biosimilars: Safety as a constant challenge

- Adverse reactions may be of any kind but adverse reactions of immunological origin arise greatest concerns.

- “Immunogenicity” is the immune system capacity to react to a foreign molecule, especially if it is a protein.

- Immune system reactions against biological medicinal products are the most critical point of safety and must be studied as a special chapter in Pharmacovigilance.

Reporting of a suspected Adverse Reaction against an innovative biotherapeutic or a biosimilar must always contain the information of the product's trademark and, whenever possible, lot number and expiration date.
Risk in the use of Biosimilars: Management

The Risk Management Plan is a document that explains the system that will be used to prevent and minimize risks in the use of a medicine. It may propose various activities in line with the same strategy.

One Risk Management Plan activity is the implementation of a patient monitoring program with participation of the entire health team responsible for administering the biosimilar. This program is called Intensive Pharmacovigilance Program.

Implementing the program is an obligation of the laboratory that markets the drug. The medical institution must take part and may control.

A program may consist in, for example, the physicians completing “clinical files” with the effects of biosimilars in patients. Then these data are processed in the laboratory databases.

The Health Authority may inspect the manufacturer and review the status of the follow-up program.

Results must be submitted to the Health Authority and may be shared with the scientific community.

Requirements for approval of a Biosimilar

Intensive Pharmacovigilance Program

Results may call for changes in the PIL, new warnings, prevention measures, etc.

Red PARF Documento Técnico No. 5 Red Panamericana de Armonización de la Reglamentación Farmacéutica. 2010.
Biotherapeutics: A new challenge for Pharmacovigilance

Innovative Biotherapeutic

The risk if an immune reaction against drug proteins restrains efficacy and affects safety.

In addition, manipulation during administration to the patient may cause use-related adverse reactions.

Biosimilars

The immune system can identify very small differences between two molecules.

Minimum differences between the reference biodrug and the biosimilar may generate an immune reaction.

Intensive Pharmacovigilance

Risk Management Programs:

A condition for marketing that is required by the Health Authority.
The active ingredient of a drug:
How the identifying name is defined

Historically, the active pharmaceutical ingredient or principle could take different names (or more than one) depending on:

- Its chemical structure
- The number and name given by the lab that developed it
- Commonly used allegorical names that survive since they were discovered
- Some agreed upon international denomination.

This situation made it possible for the active ingredient of a medicine to have more than one name. The confusion of names is one of the main causes of prescription errors.

As a result, standardization became a must. WHO and Health Agencies defined a unique denomination for each active ingredient that had to be understood by the whole world: INN, International Nonproprietary Name.

An experience in Latin America: 4 years ago, the DCA, (the Argentine Nonproprietary Name) started to be prepared with all possible synonyms of each molecule. The project took 2 years. They started with a database of 16,000 names and finally 2,600 were left.
INN: International Nonproprietary Name
The importance of a name according to WHO

Twice yearly, WHO’s INN Group of Experts meet to create and closely examine the names of new substances used in medicinal products.

The aim is to create a unique name, an INN, which doctors, pharmacists, scientists, people responsible for pharmaceutical regulations and patients may recognize and use.

“By allocating a unique international name to each medicine, WHO helps ensure that a prescription made abroad is equivalent to what a physician would have prescribed in the place of residence.” (OMS)

The name of the medicine is essential to relate clinical events to exposure.

The International Nonproprietary Name (INN) is an exclusive name that uses prefixes (as “cephalo”) or suffixed (as “pril”) as linguistic resources.

Note: DCI is the Spanish acronym for “INN”: International Nonproprietary Names
International Nonproprietary Name (INN) for biosimilars: biotherapeutic

The INN in a chemically synthesized drug is also called “generic name” and it is the name that will be used in the original and in all copies.

With a unique INN, safety analysis may be extended to the generic name of the active ingredient.

The INN of a chemically synthesized drug makes it possible to substitute one drug for another automatically.

Allocating an INN to a biosimilar would be like homologating a generic to a biosimilar, which is not correct.

We have seen that immunogenicity is a determining factor for the safety of a biotherapeutic. It should be studied in connection with the product (brand), not only the active ingredient.

On the other hand, if every biosimilar had a different name (INN) from that of the reference drug, there would be much confusion among prescribing doctors.

One possibility is to use the brand to identify the reference drug and the biosimilar. But brands may expire or be changed for market reasons, which is not the case with INN.

The brand may be an important variable in safety studies if quality aspects like determining variables, or more complex situations like adulterations or falsifications, are suspected.

When a biosimilar is administered, the brand name must be reported.

A proposal under discussion is adding a prefix to the reference drug name to distinguish it from the biosimilar.
Interchange an innovative biotherapeutic with a biosimilar: a complex decision

The exchange of an innovative biotherapeutic for a biosimilar during therapy is only possible if the doctor indicates this. It cannot be done by the patient or the pharmacist.

The most comprehensive concept is known as SWITCHABILITY, which also includes “prescribing habit” (when a doctor makes a prescription for a patient for the first time).

- **Interchangeability**: It is a medical practice consisting in exchanging one drug for another from which the same clinical effect is expected as when the patient was already receiving an active ingredient.

- **Substitution**: It is a pharmaceutical practice consisting in dispensing a drug in lieu of an equivalent pharmaceutical without asking the prescribing physician.

Health Agencies do not accept the automatic change (substitution) of a biotherapeutic for a biosimilar.

Regulación de los medicamentos genéricos: evidencias y mitos. InfTer Sist Nac Salud 2010; 34; 71-82.
Strictly speaking, substitution or interchangeability can only be guaranteed if drugs are bioequivalent for chemically synthesized products and “similar” for biological drugs (with all clinical tests proving equivalence).

Sometimes, the doctor’s decision to interchange with a biosimilar is made evident to the patient because of the emergence of an immunological adverse reaction.

In addition to clinical safety, this may result in a negative perception of the treatment.

"Guía para la implementación de estrategias de medicamentos genéricos en los países de Latinoamérica y Caribe para mejorar el acceso a medicamentos. OPS. 2011"
Summing up: key points to switch to a biosimilar.

1. Comparability: rationale supporting that they are “similar”.
2. Clinical evidence supporting the therapeutical interchangeability.
3. Cost/effectiveness studies.
4. Full assessment process of the biosimilar chosen for the switch (e.g., evaluation of clinical studies, manufacturing data, safety profile, etc.)
5. Safety monitoring (Request Intensive Pharmacovigilance program implementation by the lab marketing the biosimilar as approved by the Health Agency.)
6. Clinical response analysis after the switch.

Remember: patients must always be informed about the switch to a biosimilar.
Thank you for your attention

Time for questions and discussion